Myelodysplastic Syndromes

Peter L. Greenberg, Neal S. Young, and Norbert Gattermann

The myelodysplastic syndromes (MDS) are characterized by hemopoietic insufficiency associated with cytopenias leading to serious morbidity plus the additional risk of leukemic transformation. Therapeutic dilemmas exist in MDS because of the disease's multifactorial pathogenetic features, heterogeneous stages, and the patients' generally elderly ages. Underlying the cytopenias and evolutionary potential in MDS are innate stem cell lesions, cellular/cytokine-mediated stromal defects, and immunologic derangements. This article reviews the developing understanding of biologic and molecular lesions in MDS and recently available biospecific drugs that are potentially capable of abrogating these abnormalities.

Dr. Peter Greenberg's discussion centers on decision-making approaches for these therapeutic options, considering the patient's clinical factors and risk-based prognostic category.

One mechanism underlying the marrow failure present in a portion of MDS patients is immunologic attack on the hemopoietic stem cells. Considerable overlap exists between aplastic anemia, paroxysmal nocturnal hemoglobinuria, and subsets of MDS. Common or intersecting pathophysiologic mechanisms appear to underlie hemopoietic cell destruction and genetic instability, which are characteristic of these diseases. Treatment results and new therapeutic strategies using immune modulation, as well as the role of the immune system in possible mechanisms responsible for genetic instability in MDS, will be the subject of discussion by Dr. Neal Young.

A common morphological change found within MDS marrow cells, most sensitively demonstrated by electron microscopy, is the presence of ringed sideroblasts. Such assessment shows that this abnormal mitochondrial iron accumulation is not confined to the refractory anemia with ring sideroblast (RARS) subtype of MDS and may also contribute to numerous underlying MDS pathophysiological processes. Generation of abnormal sideroblast formation appears to be due to malfunction of the mitochondrial respiratory chain, attributable to mutations of mitochondrial DNA, to which aged individuals are most vulnerable. Such dysfunction leads to accumulation of toxic ferric iron in the mitochondrial matrix. Understanding the broad biologic consequences of these derangements is the focus of the discussion by Dr. Norbert Gattermann.

I. Controversies and Therapeutic Options in Myelodysplastic Syndrome: Biologically Targeted Approaches

*Peter L. Greenberg, MD**

Therapeutic dilemmas abound in myelodysplastic syndrome (MDS) because of the disease's multifactorial pathogenetic features and heterogeneous stages, and the patients' generally elderly ages. Underlying the cytopenias and evolutionary potential in MDS are innate stem cell lesions, cellular/cytokine-mediated stromal defects, and immunologic derangements. Given the developing understanding of biologic and molecular lesions in MDS and recently available biospecific drugs that are potentially capable of abrogating these abnormalities, specific targets are being evaluated for possible therapeutic intervention.

Goals of therapy range from symptom management/hematologic improvement (using low-intensity treatment with biologically targeted agents) to attempts at changing the natural history of the disease (generally using high-intensity treatment, including chemotherapy and hemopoietic stem cell transplantation). This review will

* Professor of Medicine, Hematology Division, Room S161, Stanford University Medical Center, Stanford, CA 94305 and Head, Hematology Section, Palo Alto VA Health Care System, Palo Alto CA 94304.

Dr. Greenberg has received research support from Amgen, Johnson & Johnson, Celgene, and Genentech.

center on decision-making approaches for these therapeutic options, considering clinical factors such as the patient's age, performance status, and risk-based prognostic category. The format for this review will be to attempt to respond to questions generally posed by patients to their physicians regarding this problematic disease, about which a great deal of uncertainty and controversy exist:

- *What is my disease?*
- *How long will I live with my disease? What problems should I anticipate experiencing? What is my chance of developing leukemia?*
- *What treatments are available for my disease? Which treatment(s) should I receive? When should I receive them?*
- *How can I learn more about my illness? Are there clinical trials with which I can and should become involved? How do I find out about them?*

What is my disease?

A. Diagnostic Classification

MDS is characterized by hemopoietic insufficiency associated with cytopenias leading to potentially serious morbidity (transfusion-dependent anemia, bleeding manifestations) and mortality (death from infection in the setting of neutropenia), plus the additional risk of leukemic transformation. The disease may arise de novo or may develop following treatment with mutagenizing agents after the patient has been treated with chemotherapy or chemoradiotherapy for other diseases (usually other malignancies). The latter variant is termed secondary or treatment-related MDS. MDS is generally relatively indolent, often with a pace of disease comprising at least several months and with a rate of progression related to a number of defined clinical features.

The French-American-British (FAB) classification initially categorized patients morphologically for the diagnostic evaluation of MDS.[1] Of importance for diagnosis is the morphologic finding of dysplastic changes in at least 2 of the 3 hemopoietic cell lines. These include megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in the early myeloid and erythroid precursors, and dysmorphic megakaryocytes.[2] MDS patients have been classified by FAB as having 1 of 5 subtypes of disease:

- Refractory anemia (RA): < 5% marrow blasts;
- RA with ringed sideroblasts (RARS): < 5% blasts plus ≥ 15% ringed sideroblasts;
- RA with excess of blasts (RAEB): 5-20% marrow blasts;
- RAEB in transformation (RAEB-T): 21-30% marrow blasts; and
- Chronic myelomonocytic leukemia (CMML): ≤ 20% marrow blasts plus monocytosis > 1000/mm^3.

CMML has been categorized as MDS, although it often has characteristics of a myeloproliferative disorder (MPD). Some groups have separated these patients into proliferative and nonproliferative/dysplastic subtypes, with prognosis being most dependent on the proportion of marrow blasts. Patients with the dysplastic form have been classified within the FAB subtypes based on their percentage of marrow blasts.

Methods are needed to enhance our ability to stratify patients by their morphologic and biologic features. Such approaches could improve prognostication and treatment for these individuals. Regarding morphologic approaches, a World Health Organization (WHO) panel has recently issued a report with proposals for reclassifying MDS,[3,4] although it has not yet been universally accepted because of certain controversial issues.[5] In this report, suggestions have been made to modify the FAB definitions of MDS. Although most prior data require at least 2-line dysplasia to diagnose MDS, the WHO guidelines accept unilineage dysplasia for the diagnosis of RA and RARS, so long as other causes of the dysplasia are absent and the dysplasia persists for at least 6 months. **Table 1** provides a comparison of the FAB and WHO classifications.

Table 1. Classifications of myelodysplastic syndrome (MDS).

FAB[1]	WHO[3,4]
RA	RA (unilineage)† 5q– syndrome‡ RCMD
RARS	RARS† (unilineage) RCMD (with RS)
RAEB	RAEB-I RAEB-II
RAEB-T	AML
CMML	MDS/MPD§
—	Unclassified

Abbreviations: MDS, myelodysplastic syndrome; FAB, French-American-British; WHO, World Health Organization; RA, refractory anemia; RCMD, refractory cytopenia with multilineage dysplasia; RARS, RA with ringed sideroblasts; RS, ringed sideroblasts; RAEB, RA with excess of blasts; RAEB-T, RAEB in transformation; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MPD, myeloproliferative disorder.

†Requires ≥ 6 months of anemia unrelated to other causes.

‡< 5% marrow blasts, micromegakaryocytes, thrombocytosis.

§MDS: WBC ≤13,000/mm^3; MPD: WBC >13,000/mm^3.

Other categories within the WHO proposal include refractory cytopenia with multilineage dysplasia (RCMD), separating RAEB patients into those with < 10% versus > 10% marrow blasts, 5q– syndrome, and MDS Unclassified. MDS/MPD has been proposed for patients who previously had been classified as CMML.

The WHO panel has also suggested excluding RAEB-T patients from MDS (proposing acute myeloid leukemia [AML] to now include patients with ≥ 20% marrow blasts, rather than the previously used 30% cut-off). However, as stated above, MDS is not only a disease related to blast quantitation, but one that possesses a differing pace related to its distinctive biologic features, in contrast to de novo AML. Recent studies have provided conflicting evidence regarding the utility of the WHO proposals.[6,7] Further studies will be needed to substantiate the prognostic value of this system.

Additional morphologic advances (e.g., degree of dysplasia, fibrosis) could provide additive information for characterizing MDS by building upon well-established forms of MDS categorization. Regarding biologic advances, as a new understanding of critical molecular, immunologic, immunophenotypic (using flow cytometry) and cytogenetic features of MDS emerges, these parameters will also be added to currently accepted methods as a means to improve the characterization of MDS.

How long will I live with my disease? What problems should I anticipate experiencing with my disease? What is my chance of developing leukemia?

B. Disease Natural History

1. Clinical features

One of the major morbidities of MDS is symptomatic anemia, with associated fatigue, which occurs in the vast majority (~60-80%) of patients. Other cytopenias may also contribute to the patient's symptom distress, including neutropenia (~50-60%) and dysfunctional neutrophils leading to an increased incidence of infections. Thrombocytopenia (~40-60%) and thrombocytopathy ensue in more advanced forms of MDS, with associated bleeding. Of importance is being alert to the potential postoperative bleeding and infectious complications that may ensue in these patients who possess dysfunctional platelets and neutrophils. Proactive management of patients' perioperative periods with relevant transfusion and antibiotic support is quite important.

With a moderate degree of variability, RAEB patients and those with RAEB-T generally have a relatively poor prognosis, with a median survival ranging from 5 to 12 months (reviewed in Greenberg[8]). In contrast, RA patients or RARS patients have median survivals of approximately 3 to 6 years. The proportion of these individuals who transform to AML varies similarly, ranging from 40% to 50% in the relatively high-risk RAEB/RAEB-T patients, and from 5% to 15% in the low-risk RA/RARS group. Regarding time-to-disease evolution, 25% of patients with RAEB and 55% of patients with RAEB-T underwent transformation to AML at 1 year; 35% of patients with RAEB and 65% with RAEB-T underwent transformation to AML at 2 years. RAEB patients with ≥ 10% blasts have poorer prognoses than do those with <10% blasts. In contrast, for patients with RA the incidence of transformation was 5% at 1 year and 10% at 2 years, and none of the RARS patients underwent leukemic transformation within 2 years.

In addition to having symptoms related to their cytopenias and need for multiple transfusions, MDS patients have major concerns about the potential for their illness to evolve into acute leukemia. Emotional stress and life-planning issues need to be addressed. All of these features lead to difficulties patients have with their quality of life (QOL).[9,10] Assessment of and engagement in the patients' relevant QOL domains—physical, functional, emotional, social, spiritual—are important for determining and potentially improving the clinical status of these individuals. Several recent studies have demonstrated the positive effects of effective therapy for MDS on patients' QOL.[11,12]

2. Prognostic stratification

Despite its value for diagnostic categorization of MDS patients, the prognostic limitations of the FAB classification have become apparent, with quite variable clinical outcomes within the FAB subgroups. The morphologic features contributing to this variability include the wide range of marrow blast percentages for patients with RAEB (5-20%) and CMML (1-20%); lack of inclusion of critical biologic determinants, such as marrow cytogenetics; and the degree and number of morbidity-associated cytopenias. These well-perceived problems for categorizing MDS patients have led to the development of additional risk-based stratification systems.[13,14]

The International MDS Risk Analysis Workshop developed a consensus risk-based International Prognostic Scoring System (IPSS) for primary MDS (**Table 2**).[14] Compared with prior systems, the IPSS has markedly improved prognostic stratification of MDS patients. In the workshop, cytogenetic, morphologic, and clinical data were combined and collated from a relatively large group of patients who had been included in previously reported studies that relied on independent risk-based prognostic systems. FAB morphologic criteria were used to establish the diagnosis of MDS.

Patients with CMML were subdivided into 'prolif-

Table 2. International Prognostic Scoring System (IPSS) for myelodysplastic syndrome (MDS).*

Prognostic Variable	Survival and AML Evolution Score Value				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5	5-10	—	11-20	21-30
Karyotype†	Good	Intermediate	Poor		
Cytopenias‡	0-1	2-3			

Risk Category	Combined Score
Low	0
Int-1	0.5-1.0
Int-2	1.5-2.0
High	> 2.5

Abbreviations: AML, acute myeloid leukemia.

* Modified from Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.

† Good = normal, –Y, del(5q), del(20q); Poor = complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities.

‡ Neutrophils < 1800/µL, hemoglobin < 10 g/dL, platelets < 100,000/µL.

erative' and 'nonproliferative-dysplastic' subtypes. Proliferative type CMML patients (those with white blood cell counts > 12,000/mm^3) were excluded from this analysis, since these individuals predominantly represented MPD rather than MDS.[15] Nonproliferative CMML patients had white blood cell counts ≤ 12,000/mm^3 as well as other features of MDS, and were included.

The most significant independent variables for determining outcome for both survival and AML evolution were found to be marrow blast percentage, number of cytopenias, and cytogenetics subgroup (Good, Intermediate, Poor) (Table 2).[14] Patients with normal marrow karyotypes, del (5q), del (20q), and –Y (70%), had relatively good prognoses, whereas patients with complex abnormalities (i.e., ≥ 3 anomalies) or chromosome 7 anomalies (16%) had relatively poor prognoses. The remaining patients (14%) were intermediate in outcome. Of the patients in the complex category, the vast majority had chromosome 5 and/or 7 abnormalities in addition to other anomalies.

When the risk scores for the 3 major variables were combined, patients were stratified into 4 distinctive risk groups in terms of both survival and AML evolution. These risk groups are Low, Intermediate-1 (Int-1), Intermediate-2 (Int-2), and High (Table 2). Median survivals and risk of MDS evolution were determined, and survival was shown to also be related to age (**Table 3** and **Figures 1** and **2**).[14] Much less precise discrimination between the 4 subgroups occurred when either cytopenias or cytogenetic subtypes were omitted from the classification. This system separated patients into relatively low-risk (IPSS Low, Intermediate-1 [Int-1]) and high/poor-risk (Intermediate-2 [Int-2] and High) prognostic groups.

Extension of this system was planned to subsequently include certain immunologic, morphologic, and molecular anomalies that would also be shown to have an impact on clinical outcomes. Flow cytometric analysis of blasts from MDS patients has provided a valuable additive prognostic tool, as demonstrated by a recent study from Japan.[16] These investigators showed that marrow blasts from most MDS patients possess a specific immunophenotypic signature

Table 3. Age-related survival and acute myeloid leukemia (AML) evolution in myelodysplastic syndrome (MDS) patients within International Prognostic Scoring System (IPSS) subgroups.*

		Median Survival (yr)			
	No. of Pts	Low	Int-1	Int-2	High
Total pts.: No. (%)	816	267 (33%)	314 (38%)	176 22%)	59 (7%)
		5.7	3.5	1.2	0.4
Age ≤ 60 yr	206 (25%)	11.8	5.2	1.8	0.3
> 60 yr	611	4.8	2.7	1.1	0.5
≤ 70 yr	445 (54%)	9.0	4.4	1.3	0.4
> 70 yr	371	3.9	2.4	1.2	0.4
		25% AML Evolution (yr)			
	No. of Pts	**Low**	**Int-1**	**Int-2**	**High**
Total pts.: No. (%)	759	235 (31%)	295 (39%)	171 (22%)	58 (8%)
		9.4	3.3	1.1	0.2
Age ≤ 60 yr	187 (25%)	> 9.4 (NR)	6.9	0.7	0.2
> 60 yr	572	9.4	2.7	1.3	0.2
≤ 70 yr	414 (55%)	> 9.4 (NR)	5.5	1.0	0.2
> 70 yr	345	> 5.8 (NR)	2.2	1.4	0.4

Abbreviations: AML, acute myeloid leukemia; pts., patients; NR, not reached.

* Modified from Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.

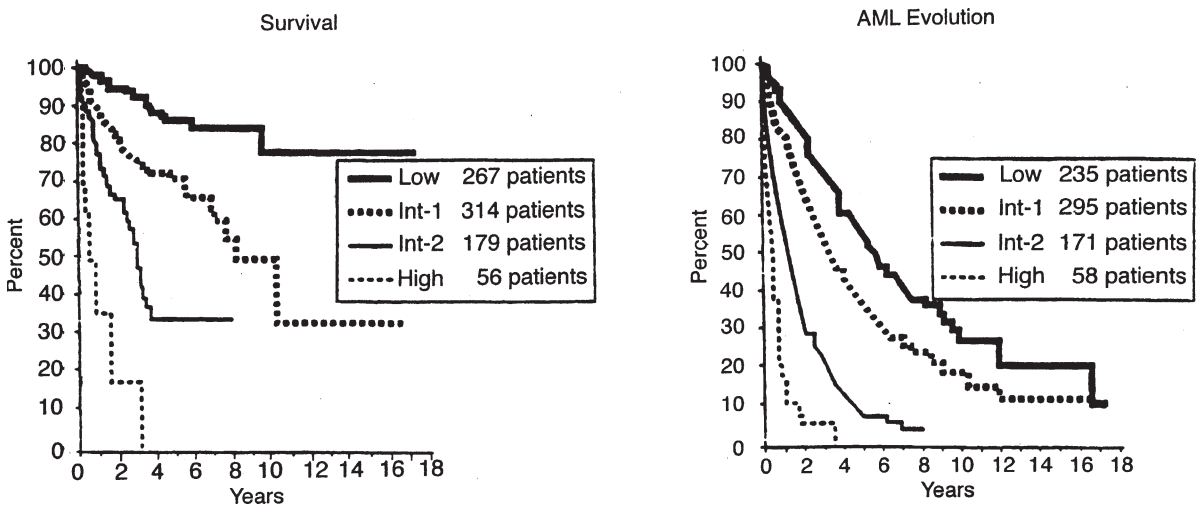

Figure 1. Survival (left) and freedom from AML evolution (right) of myelodysplastic syndrome (MDS) patients related to their classification by the International Prognostic Scoring System (IPSS) for MDS: Low, Int-1, Int-2, High (Kaplan-Meier curves). AML indicates acute myeloid leukemia.

Reprinted with permission from Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.

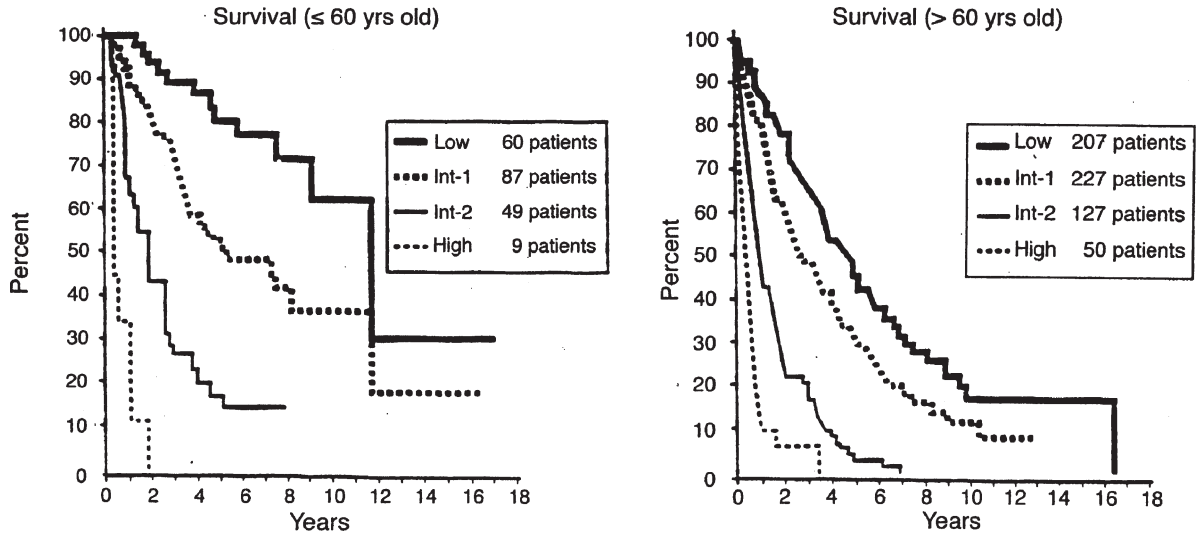

Figure 2. Survival, based on ages ≤ 60 years old (left) versus > 60 years old (right), of myelodysplastic syndrome (MDS) patients related to their classification by the International Prognostic Scoring System (IPSS) for MDS: Low, Int-1, Int-2, High (Kaplan-Meier curves).

Reprinted with permission from Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.

that is distinct from AML and normal blasts.[16] These investigators showed that a high percentage of enriched MDS blast cells had an immunophenotype descriptive of committed progenitor cells (i.e., were positive for CD34, 33, 13, 38, HLA-DR). In addition, differential expression of other surface markers on these blasts correlated with stage of disease and prognosis. Thus, the immature-type CD7 marker was generally positive on blasts from late-stage MDS patients who had poor clinical outcomes, whereas the more mature CD15 marker was generally positive on blasts from MDS patients with earlier stage disease and better prognoses. A shift occurred to a more immature phenotype accompanying disease progression. These investigators also demonstrated that RAEB-T blasts possessed immunophenotypic markers more closely related to MDS than to de novo AML, indicating that there are biologic differences between these entities.[16] Incorporation of such analyses into

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.